New Directions in Management of post-operative nausea and vomiting

Essay

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List of abbreviations

5HT	5-hydroxy tryptamine
CNS	Central nervous system
COX-2	Cyclooxygenase -2
CTZ	Chemoreceptor trigger zone
D2	Dopamine receptor
EEG	Electroencephalogram
ENT	Ear ,nose ,throat
FDA	US food and drug administration
H1	Histamine receptor
Hz	Hertz
ITN	Intubation general anesthesia
IV	Intravenous
M1-M3-M5	Muscarinic receptors
mA	Milliampere
MRI	Magnetic Resonance Imaging
NK1	Neurokinin receptor
N_2O	Nitrous oxide
NTS	Nucleus tractus solitarius
PACU	Post anesthesia care unit
PDNV	Post discharge nausea and vomiting
PONV	Post-operative nausea and vomiting
POV	Post-operative vomiting
VIP	vasoactive intestinal polypeptide

INTRODUCTION

Postoperative nausea and vomiting (PONV) defined as nausea and/or vomiting occurring within 24 hours after surgery, affects between 20% and 30% of patients[1]. Among high-risk patients, the incidence of PONV can be as frequent as 70% to 80 % [2].Nausea and vomiting are also among the most unpleasant experiences preoperatively and one of the most common reasons for poor patient satisfaction rating in the postoperative period [3].

PONV is a more hazardous post-operative complication than post-operative pain. Although the experience of postoperative nausea is generally self-limited, yet postoperative vomiting can lead to rare but serious medical complications such as aspiration especially in parturient females(mendelson syndrome), suture dehiscence, esophageal rupture (Boerhaave's syndrome), subcutaneous emphysema, or pneumothorax [4].

Many factors are commonly believed to increase the risk rate of ponv as obesity, pregnant females anxiety, use of anticholinestrase to antagonize neuromuscular blockade, and type of surgery PONV [5].

Arthroscopic surgeries, one of the orthopedic ambulatory surgical procedures, are often associated with moderate to severe postoperative pain that may require opioids for analgesia [6]. The high incidence of PONV reported after using opioids for postoperative analgesia in painful ambulatory surgical procedures suggests that alternative adjunctive analgesics may be beneficial and/or a

prophylactic antiemetic should be administered when opioids (specially morphine) are used [7].

It is not surprising that prevention of PONV in high-risk patients significantly improves postoperative ratings of well-being. Post-operative nausea and vomiting frequently delays patient discharge from post anesthesia care units and has been reported to be the leading cause of unexpected hospital admission after ambulatory anesthesia[8,9].

PHYSIOLOGY OF NAUSEA AND VOMITING

Nausea, retching, and vomiting may occur separately or together. When they occur together they are often in sequence, as manifestations of the various physiologic events that integrate the emetic reflex. Vomiting is a complex act that requires central neurologic coordination, whereas nausea and retching do not imply activation of the vomiting reflex. When nausea, retching, or vomiting manifest as isolated symptoms, their clinical significance may differ from the stereotypical picture of emesis[10,11].

Nausea :is an unpleasant subjective sensation that most people have experienced at some point in their lives and usually recognize as a feeling of impending vomiting in the epigastrium or throat During nausea, gastric tone is reduced and gastric peristalsis is diminished or absent. The tone of the duodenum and proximal jejunum tends to be increased, and reflux of the duodenal contents into the stomach is frequent.

Retching: consists of spasmodic and abortive respiratory movements with the glottis closed. When part of the emetic sequence, retching is associated with intense nausea and usually, but not invariably, culminates in the act of vomiting.

Vomiting: is a partially voluntary act of forcefully expelling gastric or intestinal content through the mouth. Vomiting must be differentiated from regurgitation, an effortless reflux of gastric contents into the esophagus that sometimes reaches the mouth but is not usually associated with the forceful ejection typical of vomiting[12].

Components

Chemoreceptor trigger zone (CTZ)

Absorbed toxins or drugs circulating in the blood can cause nausea and vomiting via stimulation of the chemoreceptor trigger zone (CTZ)[13]. The CTZ is located in the area postrema, a circumventricular organ at the bottom of the fourth ventricle **(Fig 1)**. Even though the CTZ resides anatomically in the central nervous system, its uniquely permeable endothelium (i.e., lack of a blood-brain barrier) allows it to detect emetogenic substances in the bloodstream as if it were a peripheral organ[14]. Based on a series of papers, Borison and Wang were able to demonstrate in the early 1950s that the CTZ has an abundance of receptors and that its stimulation can send emetogenic triggers to the brainstem's vomiting center to activate the vomiting reflex[15,16].

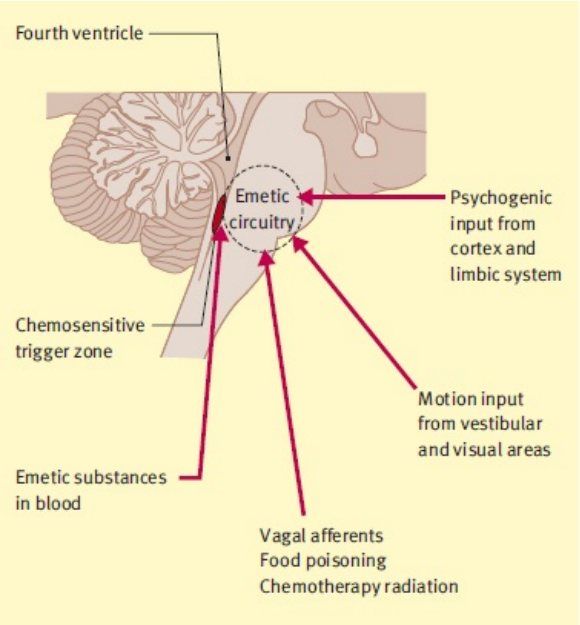

Figure1: Chemoreceptor trigger zone[17].

Although this mechanism explains how apomorphine (a fairly selective dopamine [D_2] agonist) provokes emesis, and why droperidol (a D_2 antagonist) will reverse apomorphine's emetogenic effect, it remains unclear how the CTZ

senses or transduces emetic stimuli and why nausea and vomiting are not typical side effects of dopamine infusions. Again, it remains unclear why certain receptor agonists circulating in the blood fail to trigger nausea and vomiting while corresponding receptor antagonists prevent or reduce nausea and vomiting.

Visceral afferent fibers

Ingestion of toxic substances (e.g., hypertonic saline or copper sulfate) results in the release of serotonin (5-hydroxytryptamine [5-HT]) from enterochromaffin cells in the gut wall. These enterochromaffin cells hold over 90% of the body's serotonin and appear to release it under various chemical and mechanical stimuli. Serotonin may also be released indirectly via M_3-receptors, β-adrenoceptors, and H_3-receptors; conversely, the stimulation of $GABA_B$-receptors, 5-HT_4-receptors, and α_2-adrenoceptors and the presence of vasoactive intestinal polypeptide and somatostatin have been proposed to reduce the release of serotonin[18].

Serotonin is secreted in close proximity to afferent vagal nerve endings of the gut wall that travel to the dorsal brainstem via the nucleus tractus solitarius, as demonstrated in animal models in which vagotomy blocks cisplatin-induced emesis[19]. However, large amounts of serotonin released by neuroendocrine carcinoid tumors lead to flushing, diarrhea, wheezing, and abdominal cramps but typically not to nausea and vomiting. This finding suggests that serotonergic emetogenic stimuli are primarily mediated through the autonomic nervous system rather than the bloodstream. Therefore, even though renal secretion of 5-hydroxyacetic acid (a metabolite of serotonin, with a much longer half-life) is associated with PONV after abdominal surgery a causal relationship to PONV remains unclear[20].

Vestibular apparatus (motion sickness)

The vestibular system is another source of emetogenic stimuli, as observed in motion sickness or Meniere's Disease[21,22]. Motion sickness is a risk factor for PONV. whether vestibular input contributes to the emetogenic state in the vomiting center or whether anesthetics or opioid analgesics contribute to the susceptibility of the vestibular organ or signal processing is not clear[23,24].

Central nervous system

Various psychic stimuli including disquieting scenes, noisome odours, and other similar psychological factors can cause vomiting. Stimulation of certain areas of the hypothalamus also can cause vomiting. The precise neuronal connections for these effects are still not known, although it is probable that the impulses pass directly to the vomiting center and do not involve the chemoreceptor trigger zone[25].

Vomiting center

Final common pathway of vagus & phrenic nerves located in the lateral reticular formation of the medulla . Electrical stimulation of this site triggered the vomiting reflex, whereas ablation prevented the vomiting induced by a variety of stimuli. The vomiting center was thought to be located adjacent to the other structures involved in the coordination of vomiting, including the respiratory, vasomotor, and salivary centers, and cranial nerves VIII and X. More recent studies have suggested that the “vomiting center” is actually not anatomically discrete but that the initiation of the vomiting reflex is controlled by a complex system of networks located in the nucleus tractus solitarius.[26] The networks in this area control complex patterns of motor activity such as the vomiting reflex and are more accurately described as “central pattern generators.”

This center receives abdominal afferents (from GIT and outside GIT) as well as afferents from several areas within the central nervous system, including the chemoreceptor trigger zone, vestibular apparatus, cerebellum, higher cortical brainstem centers, and solitary tract nucleus. These structures are rich in dopaminergic, muscarinic, serotoninergic, histaminic, and opioid receptors, and block of these receptors may be the mechanism of the antiemetic drugs[27]. At the present time, there are no drugs known to act directly on the vomiting center. However, a new class of antiemetic drugs (Neurokinin (NK_1) receptor antagonists) may act on the final common pathway from the vomiting center, as this class of drugs has been shown to provide protection in animal models against emetogenic stimuli from motion, cisplatin, irradiation, morphine and copper sulphate[28].

Miscellaneous inputs

Nausea, and gagging in particular, can be evoked readily by mechanical stimulation of pharyngeal afferents projecting to the brainstem in the glossopharyngeal nerve [29].

Ventricular cardiac afferents may induce nausea and vomiting in man and experimental animals, and their activation probably accounts for these symptoms (particularly nausea) before, or in association with, myocardial infarction.

Coordination of the components of the vomiting reflex

This coordination occurs in the brain stem. The vagal motor neurons supplying the gut and heart originate in the dorsal motor vagal nucleus and nucleus ambiguous. In addition, the dorsal and ventral respiratory groups regulating the phrenic nerve output from the cervical spinal cord are located in the brainstem as are the presympathetic neurons which maintain sympathetic tone to the heart and blood vessels. The output of these nuclei must be

coordinated to produce the characteristic vomiting pattern. A promising candidate for this task is the nucleus tractus solitarius. This is probably the major integrative nucleus for visceral afferent information and, in addition, the ventral portion forms the dorsal respiratory neuronal group involved in the regulation of respiration [30].

The act of vomiting involves a series of motor events involving both autonomic and somatic divisions of the nervous system **(Fig 2)**. These motor events can be classified into two separate but usually consecutive phases: *pre-ejection and ejection phases.*

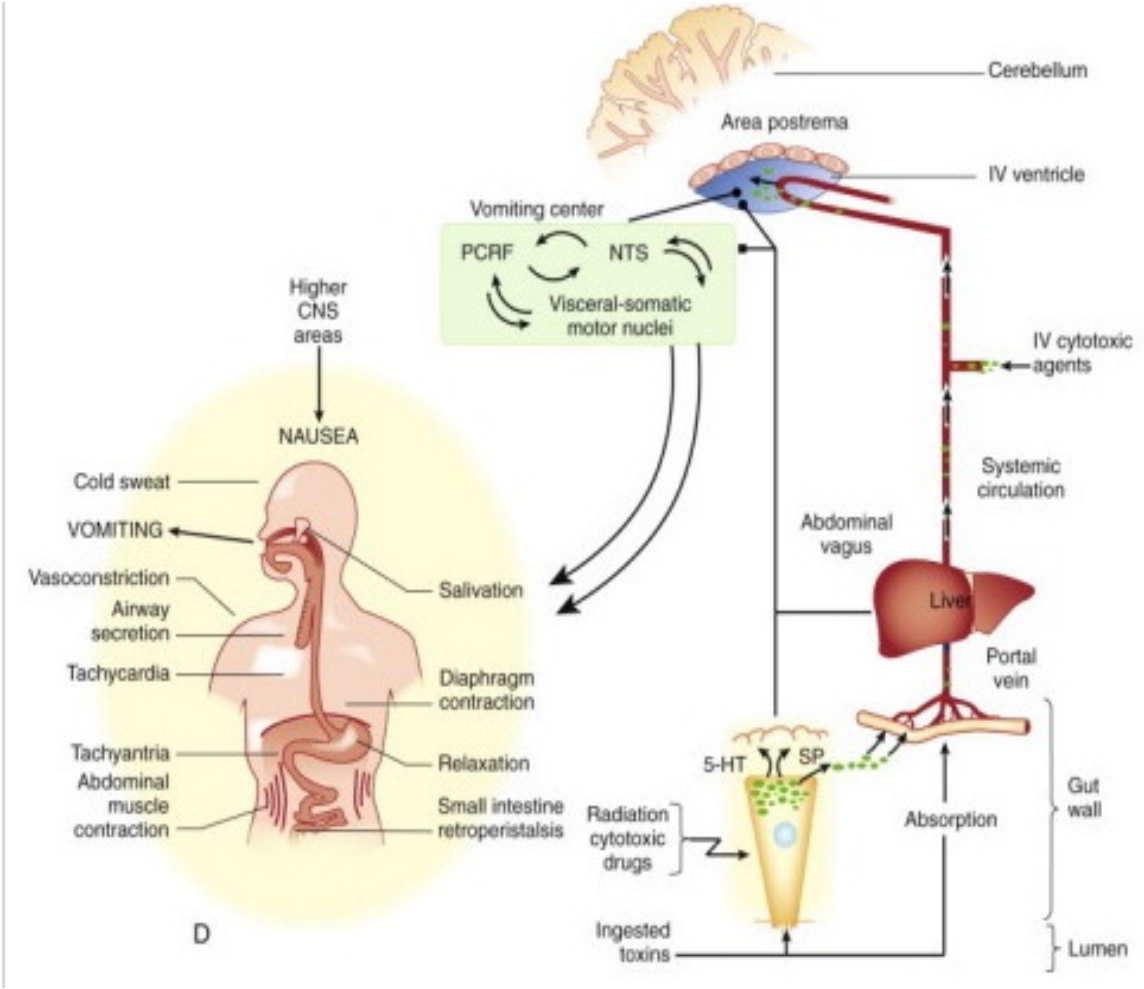

Figure 2: organization of the emetic reflex[16].

Pre-ejection phase

The pre-ejection or prodromal phase is characterized by the sensation of nausea, There are several visible signs such as cold sweating, cutaneous vasoconstriction and pupil dilatation mediated by sympathetic nerves and salivation mediated by parasympathetic nerves. In addition, changes occur in visceral function such as tachycardia and a reduction in gastric secretion, both mediated probably by sympathetic activation. Immediately before the onset of the ejection phase there is profound relaxation of the proximal stomach mediated by vagal efferent nerves activating postganglionic neurons in the stomach wall.

These neurons probably use vasoactive intestinal polypeptide (VIP) or nitric oxide as neurotransmitter. In conjunction with this, a retrograde giant contraction originates in the mid-small intestine and travels towards the stomach. The retrograde giant contraction is under vagal control and the transmitter involved is acetylcholine. These two gut motor events are of particular interest as they can be argued to have a clear function in the reflex - the gastric relaxation serving to confine orally ingested toxin to the stomach and the retrograde giant contraction returning any contaminated gastric contents to the stomach ready for ejection.

Ejection phase

This phase comprises retching and vomiting with oral expulsion of gut contents only occurring during vomiting. Both retching and vomiting involve principally contractions of the somatic muscles of the abdomen and diaphragm. During retching the abdominal muscles and the entire diaphragm contract synchronously whereas during vomiting the peri-oesophageal diaphragm